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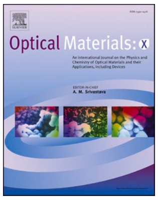

(INVITED) Flexible photonics for biomedical applications: A review

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ABSTRACT

Flexible photonics is a powerful tool that has emerged in last few decades to solve footprint and shape related limitations in photonic devices. Indeed, flexible photonic devices offer several key features: ability to adjust to complex shape surfaces, small footprint, high resilience to mechanical damage, immunity to electromagnetic interference. Thanks to these characteristics, these devices are very attractive for applications in the biomedical field. For instance, the flexibility allows optimal adhesion to the skin, or the reduced size facilitates the realization of wearable devices. In this paper, we will first present the characteristic of flexible photonic devices and discuss about the so far impact of flexible photonics in the biomedical field. Then, we will analyze the currently existing devices and the main used components, with a focus on the applications.

1. Introduction

In the past two decades, the incorporation of flexibility into the photonic field has paved the way for many new opportunities. This is because the purpose of flexible photonics is to replace rigid and bulky components with novel materials, better suitable for specific needs, and that can withstand mechanical stress. This results in photonic devices that (1) are less susceptible to mechanical damage, (2) can fit better on irregular surfaces and/or spaces, and (3) are usually smaller in size compared to their rigid counterparts [1–5]. Due to these characteristics, interest in flexible photonics has grown significantly, before settling in recent years. Fig. 1A shows this trend. The histogram in Fig. 1A was obtained by investigating Scopus [6] data, and the used search criteria were: the article must contain the word (1) “flexible” in the title and (2) “photonic” or “photonics” in the title, abstract or keywords. Since flexibility is the key feature, the novelty over existing devices, we decided that it had to be contained in the title. Instead, photonics is the field of application, not the new feature, so we allowed that it could not be in the title, but at least in the abstract or keywords.

The rise in popularity of flexible photonics has attracted the interest of the biomedical field [2,5,7,8]: indeed, among all previous characteristics, several are very appealing for practical biomedical devices. First of all, and also the one currently most exploited, a flexible device could be attached to an extremely complex surface such as the skin [9–13]. Indeed, it not only has an irregular surface but also stretches in various directions during a movement, mechanically stressing any device attached to it. Among the several possible devices that benefit from this feature, the most notable are wearable devices [9–17]; in order to be “wearable”, they have to withstand the countless movements that a person performs in everyday life. Furthermore, optical devices are not susceptible to electromagnetic fields under normal conditions [3–5,18,19]. However, in strong magnetic field areas like MRI (Magnetic Resonance Imaging) they may suffer, so the active part of the device may be required to be remotely located while the passive part (e.g., fiber optic) can go inside the MR [20–23]. If needed, a photonic device can monitor specific patient parameters (e.g., breath rate) during the MR examination [20–23]. Or perhaps, a photonic device could be used to integrate MR images. Last, a device based on flexible optics will have a low power consumption [5]; this is beneficial for wearable devices, as they may have to be active for long times (e.g., all day long [13]).

All of the above are just some of the possible benefits that flexible photonics can bring into the biomedical field. To assess the impact of flexible photonics in the biomedical field we therefore looked at published research papers. Fig. 1B shows that biomedical flexible photonics is still at its early growing phase, and it is not yet very popular. The histogram in Fig. 1B was obtained by adding a third rule to the previous two used in Fig. 1A: the article shall discuss an application in the biomedical field. We required at least one of the following words to be included in the title, abstract, or keywords: “medical”, “medicine”, “diagnostic”, “biomedical”, “biomedicine”, “biology” or “clinical”. As can be seen from the graph, the trend in the biomedical field is comparable with that from flexible photonics before about 2004. At last, while flexible photonics seems to have reached a plateau (Fig. 1A), applications in the biomedical field have a positive trend (Fig. 1B), which is likely to grow further in the next years.

In this review we will focus on the currently existing flexible

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photonics devices for biomedical applications. The purpose is to show which applications are the most popular, and consequently which areas are not addressed yet. Also, for each application, it is interesting to observe which different solutions have been proposed, and which are main advantages and disadvantages. Therefore, the aim is to further stimulate interest in the topic, since there are still many solutions to be explored. However, we will not go into detail about the materials used, as they mainly are polymers that are already very well known in biomedicine [24–30], such as: polydimethylsiloxane (PDMS) [16,18,19,31–33], polylactic acid (PLA), polyglycolic acid (PGA), poly (lactic-co-glycolic acid) (PLGA) [34,35], polytetrafluoroethylene (PTFE) [17,36], polyethylene glycol (PEG) [17,37–39], polyethylene terephthalate (PET) [13], polymethyl methacrylate (PMMA), polyurethanes (PUs) [9], polyimides (PIs) [10,15], and epoxy [12]. Moreover, for what concern materials and fabrication methods for photonic devices, there are already many reviews with a focus on this topic [1–5,7], so this paper will discuss mainly the applications and the peculiarities of each flexible photonic devices.

2. Devices, components and applications

Before mentioning the flexible photonics devices currently existing in the biomedical field, it is worthwhile to clarify which devices we have classified as such or not. In this review, optoelectronic devices will be considered as photonic devices, since both work through optical phenomena; even other research groups made no distinctions between the two types [2,5]. Devices will therefore include photonic components such those that can generate (e.g., laser sources) and/or manipulate (e.g., optical amplifiers, waveguides) photons [4,5], as well as optoelectronic components such photodiodes (PDs), LEDs (Light-Emitting Diodes) or OLEDs (Organic LEDs) [2,4,5]. Moreover, we decided to exclude flexible SERS (Surface-Enhanced Raman Spectroscopy) devices from flexible photonic devices, even though they are included in other reviews. Very briefly, SERS is Raman spectroscopy that exploits specific substrates (e.g., silver or gold nanoparticles that can generate surface plasmons) to amplify the Raman signal, typically lower in intensity. To the best of our knowledge, in all flexible SERS papers, the only flexible component is the substrate responsible for the plasmonic effect; instead, both the light source and the detector are rigid and distinct from the flexible component [40–43]. This is the main reason these papers will not be covered in this review.

Regarding general structure of biomedical photonics devices, in almost all of the works found, the light source is a LED (or an OLED) [9–12,15–17,44], with emission wavelength in the visible or near-infrared range. Since in the papers in this review the only relevant parameter used to detect is to look at light amplitude variations a PD as detector is used [9–12,15–17,44]. Some of the works reviewed use only these two optoelectronic components, while others also develop optical waveguides [11,14,16,18,19,34,45]. Their primary and essential characteristics are flexibility and biocompatibility, since they are used in biomedicine. Not all the devices in this review are biocompatible in the same way: most of them are placed on the skin while few of them are placed partially inside the human body; the external devices are just required to be non-toxic and non-irritant for the skin, while the implantable ones have additional requirements that will be described below. In most cases, these waveguides are made directly with polymeric materials, most notably PDMS [16,18,19,31–33]. Indeed, it is not only suitable as an optical waveguide thanks to its optical properties [30,46], but it also possesses excellent flexibility, reaching 150% strain [18], and well-known biocompatibility [2,29,30,47]; moreover, PDMS is resistant to biodegradation, retaining its shape even if implanted, and can be produced by replica molding, a simple fabrication method [29,30]. Besides PDMS, optical waveguides can be made using materials such as TiO_2 [5,45,48] or SiO_2 [48]. Lastly, Liang et al. [14] stretched a standard single-mode optical fiber with a flame-heated technique to obtain a biconical tapered fiber with a diameter of 1.8 μm in the stretched part.

2.1. *Pulse oximetry devices*

Most devices in the biomedical field belong to the category of pulse oximetry [49,50]. This class of devices extracts several human vital signs by monitoring blood oxygen saturation [49,50]. The value of this parameter indicates, as a percentage, the amount of oxygenated hemoglobin in the blood compared to the total (both oxygenated and deoxygenated) at a given time. As a result, by monitoring its cyclic variation over time, several other physiological parameters can be obtained, such as heart rate as shown in Fig. 2B. For instance, Bae et al. found that breath (e.g., sighs, coughs) and temperature variations can affect the blood oxygen saturation signal.

Pulse oximetry devices are typically based on two light sources, a red LED in the range 620–660 nm and a near-infrared (NIR) LED in the range 850–950 nm (Fig. 2B) [9–12]; instead, some research groups replaced the NIR LED with a green LED at 520–532 nm [13,44]. The light should pass through a thin enough part of the human body, usually through the fingertip or through the earlobe. Then, the light is collected on the opposite side (transmitted light [11,44]) and is converted to an electrical signal, using a PD. Instead, some devices have the PD placed near the LEDs, so they can collect reflected light [9,10,12]; in such cases, the device can also be placed in other parts of the body (e.g., wrist) [9].

Nowadays, pulse oximetry devices are bulky and rigid, and are usually clipped to the fingertip; thanks to flexible photonics, it is possible to reduce its size. Indeed, flexible devices are about the size of a button or a nail, some are even smaller (Fig. 3D–F); they can be applied like a patch (Fig. 2D), reducing the size and allowing any kind of movement. Moreover, their performances are comparable with that of the rigid devices currently in use.

Lochner et al. [44] realized a simple device, in which optoelectronic

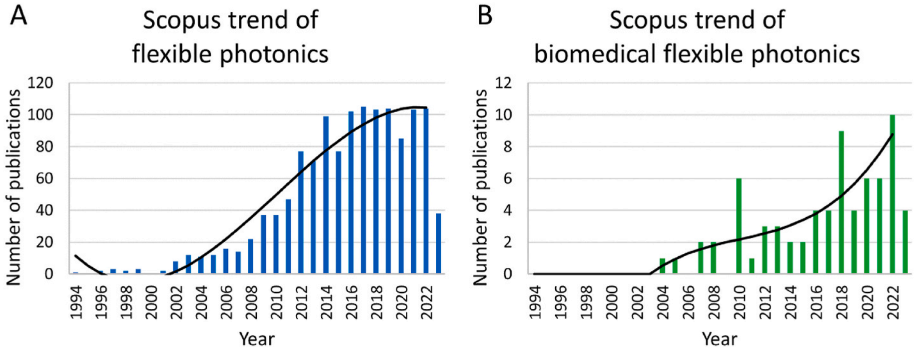

Fig. 1. **A)** Number of flexible photonics publications through the years with a polynomial fitting of the 3rd order. **B)** Number of flexible photonics publications related to biomedical field through the years with a polynomial fitting of the 3rd order.

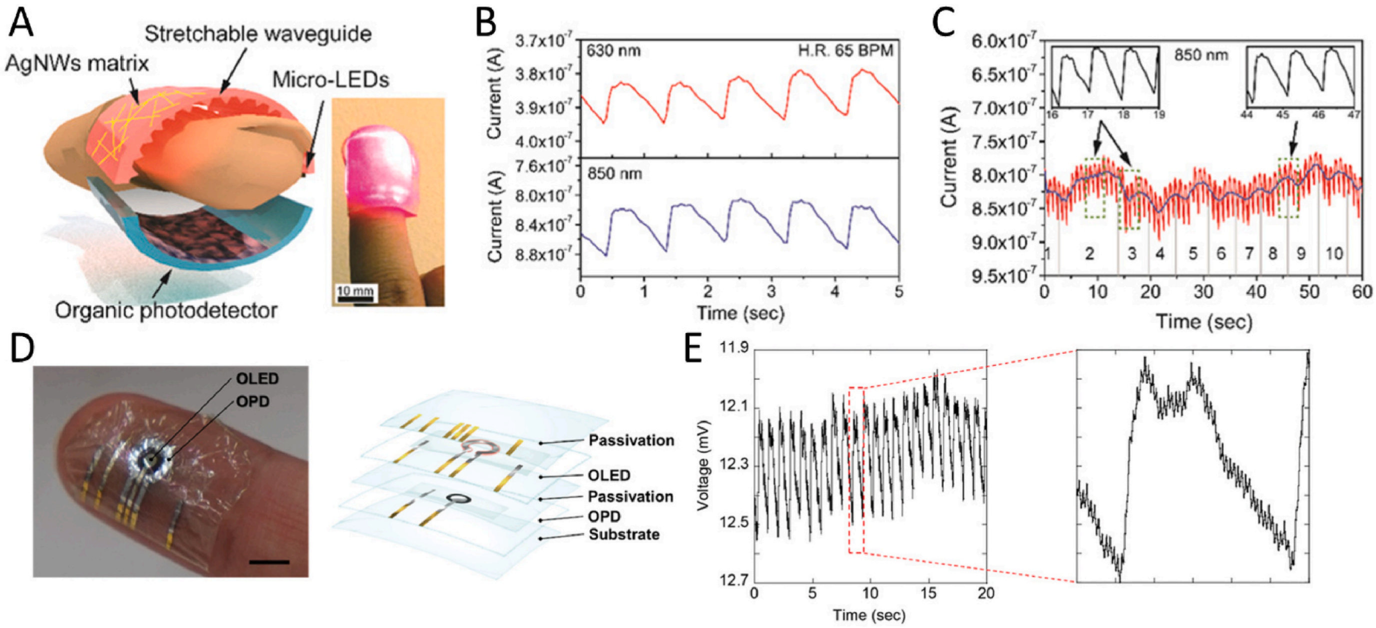

Fig. 2. A-C) Figure from Bae et al. paper. Reprinted (adapted) with permission from Ref. [11]. Copyright 2023 American Chemical Society. **A)** Flexible photonic device for pulse oximetry developed in the work. **B)** Example of pulse oximetry signal: the two signals collected by the PD from the red LED (630 nm) and the NIR LED (850 nm). The signals change in a cyclic way based on the blood oxygen saturation, so it is possible to calculate the heart rate (top right corner). **C)** Effect of breathing on the pulse oximetry signal. Through the monitoring of many signal cycles, it is possible to determinate the breathing cycles of the patient. **D-E)** Figure from Yokota et al. paper. Reprinted (adapted) with permission from Ref. [12]. Copyright 2023 John Wiley and Sons. **D)** Flexible photonic device for pulse oximetry developed in the work. **E)** Example of pulse oximetry signal. It changes in a cyclic way based on the blood oxygen saturation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

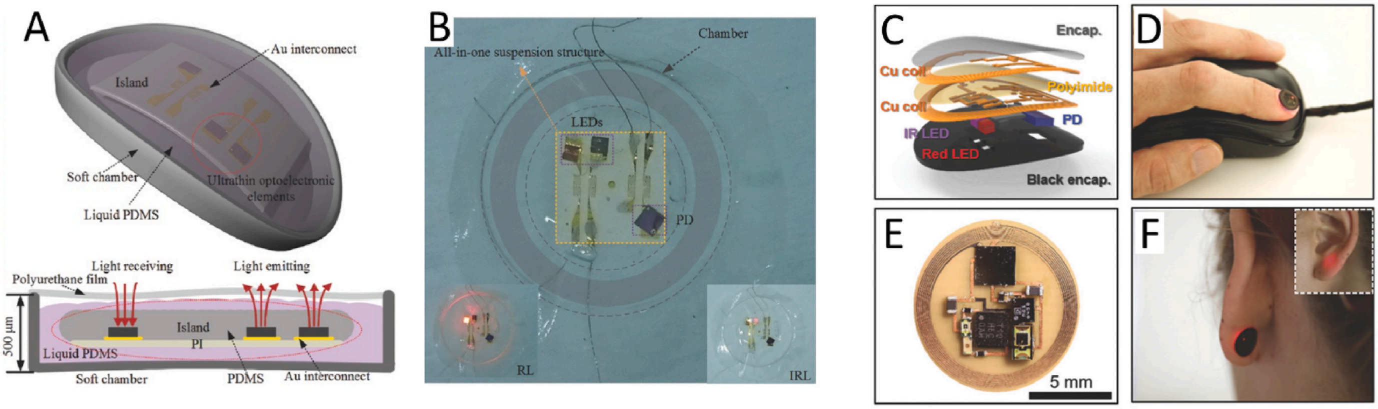

Fig. 3. A-B) Flexible photonic device for pulse oximetry developed by Li et al. Reprinted (adapted) with permission from Ref. [9]. Copyright 2023 John Wiley and Sons. C–F) Figure from Kim et al. paper. Reprinted (adapted) with permission from Ref. [10]. Copyright 2023 John Wiley and Sons. **C)** Scheme of the flexible photonic device for pulse oximetry developed in the work. **D)** Example of the device applied on the nail. **E)** Dimension of the device realized. **F)** Example of the device applied at the earlobe.

components (LEDs and PDs) are placed on a circular substrate of flexible plastic. Then, transmission blood oxygen saturation can be monitored by inserting the fingertip inside the device. From the comparison with a commercially available device, it emerged that there were some inaccuracies, probably due to motion artifacts. Instead, other research groups realized button-like devices based on reflection (Fig. 3) [9,10,12,13]; in this case, optoelectronic components are embedded in a flexible tridimensional structure, that can be attached to any part of the body. In addition, Kim et al. [10] built a completely wireless device by integrating an NFC chip. Last but not least, Bae et al. [11] realized a distinctive transmission pulse oximetry device (Fig. 3A): instead of placing the LEDs directly on the skin, they made a planar optical waveguide that spreads out the light transversely. The flexible sheet-like optical guide is applied on the top of the fingertip; the light passes through the guide and spreads out uniformly in the direction of the finger, crossing it. On the other side of the finger, an organic PD collects light. Like the previous one, it is wireless too, but uses Bluetooth to communicate data externally.

2.2. *Optical waveguide sensor and motion analysis*

Some devices employ optomechanical effects to convert a mechanical stimulus into a detectable optical signal variation [51]. The devices in this review are based on an optical fiber that can be mechanically deformed (i.e., stretched [16,18,19] or bended [14]), causing a variation in the intensity of the light that pass through the fiber. A deformation in a fiber could generate a variation also in other parameters of the light, such as the phase or the polarization; however, the following devices monitor only the optical intensity with a PD, because of lower cost and far simpler setup with respect phase sensitive detection schemes. The light passing through an optical fiber is attenuated due to the absorption of the material and due to other loss phenomena (e.g., a sharp bending). The absorption will be greater as the optical path increases; if an optical fiber is stretched and if its density remains constant [19], the optical intensity at the fiber output will be lower [16,18,19]. In the works that will be presented in this section, the other loss phenomena are negligible. For example, fiber stretching causes also a reduction in the diameter, and the modal transmission may change; however, these fibers have a diameter from 0.5 mm [16,19] up to 1 mm [18], are polymeric, and are presumably multimodal, so such effect should be negligible compared to absorption. Concerning the absorption, usually optical fibers have to achieve an optimal transmission of the light, thus they are made of materials with very low attenuation, expressed in dB/km. Therefore, the light passing through a conventional optical fiber is not sensitive to small changes in length: an increase in length of the order of kilometers would be necessary to appreciate a difference in the output optical intensity. In order to make fiber optic sensors able to detect changes of the order of millimeters, it is necessary to use a material with a significant attenuation. In order to achieve this result, the works reported below employ polymer fibers made of PDMS or photocurable resin [16]; in some cases, other materials have been dispersed within the polymer matrix (i.e., gold nanoparticles (GNPs) [19] and graphene powder [18]) to further increase the attenuation and thus the sensitivity to fiber length variation. Table 1 reports the attenuation values of these types of fiber and the stretching resolution achieved; the attenuation is expressed in dB/cm, much larger than conventional fibers (dB/km).

Therefore, it is possible to monitor the stretching of the fiber in real time by connecting a light source and a photodetector to its two ends and analyzing the changes in the intensity of the light. Thanks to this feature, these devices can be used to analyze and monitor the movement of a human body part. For instance, movements made by the hand can be monitored by attaching fibers to the backs of open fingers; closing a finger will stretch the fiber, and thus the optical intensity obtained from the fiber will drop, recording the movement (Fig. 4B) [18,19]. They can also retrieve physiological signals, such as heart and respiratory rates. In the first case, the signal can be obtained, for example, by measuring the pressure on the wrist caused by the passage of blood (Fig. 4C) [14,19]; indeed, the blood flow bends the fiber at the heart rate, changing the optical intensity signal. While in the second case, breathing can be monitored by measuring expansion/contraction of the rib cage [16,18]; for example, a fiber fixed around the rib cage will stretch with each inhalation and will relax with each exhalation, changing the output of the fiber. Movement analysis can be used, for example, to monitor pathological situations (e.g., Parkinson's disease [19,51]). Thanks to flexible photonics, it is possible to design wearable systems that can be used outside a laboratory, in everyday life; also, as mentioned earlier, the main advantages would be smaller size and lower power consumption. Instead, heart and respiratory rate sensors can be used, for example, to monitor patients during MRI examinations.

Table 1
Characteristic of optical fiber sensors sensitive to small stretching. The spatial resolution of the sensor made only of PDMS has not been tested in the papers under examination. The spatial resolution of graphene-PDMS has been tested only up to a certain value, so probably it could be lower than the value reported.

Fiber Materials	Attenuation (dB/cm)	Spatial Resolution (mm)	Reference
Polydimethylsiloxane (PDMS)	0.32–0.63	Not tested	[18,19]
Graphene-added PDMS	2.58	3.00	[18]
PDMS with gold nanoparticles (GNP-PDMS)	5.47	0.05	[19]
Photocurable resin	7.00	0.02	[16]

For instance, Wang et al. [18] proposed a graphene-added PDMS fiber. Due to the properties of PDMS, the fiber is able to reach 150% strain. The addition of graphene powder, dispersed in PDMS, produces a fiber with a larger loss absorption coefficient (2.58 dB/cm), and thus significantly higher sensitivity when compared to the PDMS only fiber (0.63 dB/cm). The device has been tested both for motion analysis and breathing monitoring. In the first case, it was placed in different parts of the body subject to bending (i.e., along the back of the finger, on the wrist, on the elbow, and on the knee), successfully discriminating movements, even the small ones (tested up to 3 mm of stretching); the fiber was also placed around the forearm, correctly detecting the increase of the diameter due to muscle contraction. Instead, to monitor respiration, the fiber was placed around the abdomen, successfully identifying the inhale/exhale phases. Guo et al. [19] developed a similar device, but instead of using graphene, they dispersed gold nanoparticles (GNPs) within the PDMS (Fig. 4A); the purpose is the same as with graphene, but in this case, they exploited the plasmonic effect of GNPs to increase the loss of the fiber (5.47 dB/cm). Here, the maximum strain is 100%, and the device can sense a minimum displacement of 0.5% (0.05 mm). Once again, the device was tested with finger movements by placing five fibers (one on each finger) (Fig. 4B). Furthermore, by placing the fiber on the radial artery of the wrist, they have been able to measure blood pressure and heart rate (Fig. 4C). Finally, by placing the fiber anteriorly on the neck, they obtained different signals during swallowing or speaking of different words (Fig. 4D). Instead, Leal-Junior et al. [16] proposed a different shape for the device: instead of a single linear fiber, a system of fibers arranged in an orb-web design, with a single light source in the center and the PDs around the edges. The fiber is composed of a photocurable resin core and a PDMS cladding, reaching an attenuation of 7 dB/cm and a resolution of 0.02 mm. The main advantage is the capability to track multiple directions with a single device; in fact, they monitored the movement of all the fingers by placing the sensor on the back of the hand. Moreover, they have integrated the device into clothing and placed it at the chest; thus, the sensor can detect both respiratory rate and simple trunk movements.

Lastly, Liang et al. [14] developed an optical fiber that can detect bending, instead of stretching. Through a flame-heated technique, they stretched a standard single-mode fiber up to 1.8 μm of diameter; then, they embedded the μ-fiber into a PDMS substrate. This sensor takes advantage of a different mechanism, the self-mixing interference. The bending of the fiber causes a leakage of the light, so the optical intensity drops. By placing the sensor on the radial artery of the wrist, heart rate and blood pressure can be monitored.

2.3. Implantable devices and components

Besides those two categories, there is another class of devices: we classified them as implantable devices, because, compared with the previous ones, these have been designed with features that allow them to be placed totally or partially inside the human body. In the following works, all devices are partially implanted, so they are composed of an external unit and an internal probe, inserted subcutaneously. Previous devices, which were also classified as biocompatible, were only biologically inert and nontoxic in contact with the skin. Instead, an implantable device needs also other characteristics in order to ensure proper functioning without affecting the patient's health. For instance, the material may be biodegradable and bioabsorbable, meaning that the human body is capable of degrading and eliminating it naturally; an example is the PLGA, a polymer that within the body is degraded into lactic acid and glycolic acid, compounds that are cleared by the renal system [34,35]. In this way the removal is not necessary; for example, a biodegradable device can be useful for surgery in order to monitor healing, because they can be placed even where subsequent removal would be problematic. Or, the device can be coated with an anti-fouling material, which prevents protein adsorption and cell adhesion; an example is the PEG, a polymer well known for its properties in the

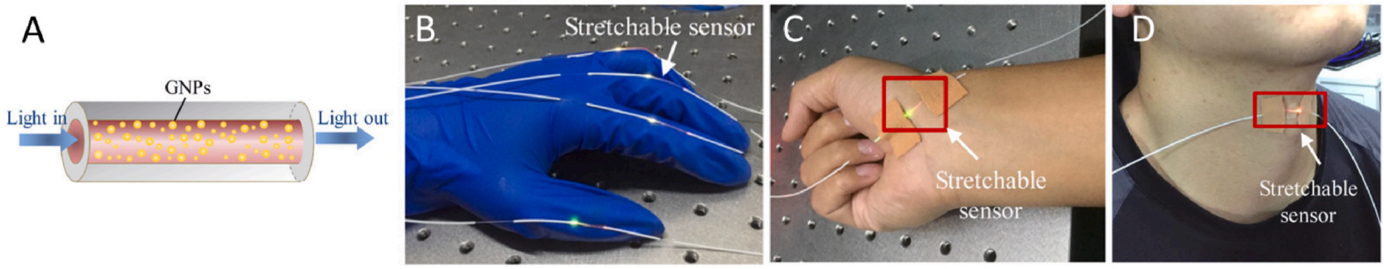

Fig. 4. A-D) Figure from Guo et al. paper. Reprinted (adapted) with permission from Ref. [19]. Copyright 2023 American Chemical Society. **A)** Fiber designed, with GNs dispersed into the PDMS matrix. **B)** Strain sensors fixed to the fingers to monitor the hand movements. **C)** Strain sensor fixed to the wrist to monitor blood pressure. **D)** Strain sensor fixed in front of the neck to analyze movements related to phonation or deglutition.

biomedical field [17,37–39]. This property is fundamental for devices that should be left inside the human body for a long period of time, as any covering of proteins or cells can affect their correct functionality; in addition, the anti-fouling coating provides biomimetic properties, preventing the recognition by the immune system and the subsequent failure of the implant.

Bai et al. [34] made an implantable NIR optical waveguide composed of totally biodegradable and bioresorbable materials; in detail, the guide is made of a monocrystalline silicon core and a PLGA cladding. The implantable optical waveguide can be used for NIR spectroscopy analysis directly in the area of interest, to monitor relevant biomolecules, such as glucose. In the paper, the fiber has been tested subcutaneously in a mouse and has been used to obtain data related to blood oxygenation. In addition, the *in-vivo* experiment demonstrated the non-toxicity of the optical guide and its biodegradability, disappearing completely in 15 days.

Nguyen et al. [17] also proposed an implantable device to monitor biological analytes, in this case for pH and lactate detection. The device consists of a rigid external unit to be fixed to the skin and a flexible subcutaneous probe. The external part contains photodetectors and the circuitry required to work. The probe has to be placed below the external device, and is coated with biocompatible, non-toxic, non-fouling materials such as PEGDMA (poly (ethylene glycol) dimethacrylate) [37] and PTFE [36]. The probe contains also the LEDs needed for analysis, one at 400–465 nm with a pH-sensitive fluorescent sheet on it for the pH value, and the other at 625 nm with an oxygen-sensitive phosphorescent sheet for lactate concentration. This second particular sheet also contains an enzyme (i.e., lactate oxidase) that can consume lactate and oxygen, producing hydrogen peroxide and pyruvate; therefore, if lactate is present, the enzyme consumes oxygen, and this variation is detected by the oxygen-sensitive sheet. Last, another LED and another sheet are used as a reference to quantify the lactate concentration. In the work, both in vitro and in vivo (rabbit) tests are performed, using another device for comparison. The proposed device correctly identifies pH values between 6.92 and 7.70, discriminating the anomalous situations of acidosis (<7.35) and alkalosis (>7.45); moreover, it can monitor lactate concentration up to 9 nM (normally around 1–2 nM).

Zhao et al. [45] developed a flexible temperature sensor that can be implanted to monitor, for example, deep brain temperature or wound temperature. The sensor is made of SU-8 polymer, a common epoxy-based negative photoresist, with inside photonic circuitry of TiO_2, that is generated by lithography. The TiO_2 shapes a micro-ring resonator, which is the sensing element: a variation in temperature results in a shift in the resonant frequency. The sensitivity obtained is −195.9 pm/°C, higher than, for example, silicon (80 pm/°C).

Instead, Liu et al. [48] proposed an implantable component with a different application. Indeed, they developed an implantable thin-film optical filter composed of two layers, one of TiO_2 and the other of SiO_2. In-vivo tests (in rats) were conducted to test its biocompatibility, demonstrating non-toxicity and absence of pathological inflammation. In this specific paper, a filter with a passband from 560 nm to 620 nm was created for the sake of example, with very good performance: transmittance in the passband greater than 90% and near-unity reflectance (>99%) in the stopband. However, the designed object is not an actual device, but is a flexible optical filter that can be used to improve the performance of an implantable optical device.

3. Discussion and conclusion

Flexible photonics has started to receive attentions from various research groups about two decades ago and has become very popular in the last decade. Its applications space multiple fields, and one of the most promising is the biomedical field yet in its infancy (compare Fig. 1A and B) [1–5,7,8]. Indeed, flexibility in photonic devices can be very beneficial in this field [2,5,7]. The main and most exploited advantage is the opportunity to realize devices that can adapt to the irregular surface of the skin, and that can withstand the associated mechanical stresses. Wearable devices, whether attached to the skin or integrated into clothing, permit more efficient and less bulky monitoring. In addition, as mentioned previously, the flexibility and biocompatibility properties of the materials used also allow the development of implantable optical devices. Probably the lack of papers so far is because it is still in an embryonic stage, not a lack of interest; actually, although the number of publications is very low, the trend over the years is definitely growing, and we predict it will become very popular in the next few years. Furthermore, by analyzing the journals in which papers are published, it can be seen that almost all of them are in materials, sensor or related to optics. Perhaps biomedical research groups are not yet involved in device testing of flexible photonics and therefore are not yet aware of its advantages.

In addition, so far, the applications are still limited to very specific fields (e.g., pulse oximetry). Certainly, in the future there will be an expansion and an improvement of the few applications shown in this review. Nevertheless, it would be interesting to see flexible photonic devices in a wide range of biomedical applications. For example, there could be many specific devices to be used during MR examinations. Also, more devices focused on the monitoring and analysis of pathological conditions, such as Parkinson's disease. Flexible photonics could also be helpful outside health monitoring, for instance in patients with eyesight defects (e.g., artificial retina), or even in patients with tactile detects or prosthetic implants (e.g., artificial skin, tactile sensors). These are just few of the many possibilities not yet explored, since flexible photonics has beneficial capabilities for many areas of biomedicine.

CRediT authorship contribution statement

Riccardo Ballarini: Writing – original draft, literature research, discussion. **Stefano Taccheo:** planning, discussion, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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